Exhibit G

TECHNOLOGY, COMPUTING, AND SIMULATION
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Resistive-Heating and Forced-Air Warming Are Comparably Effective

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Serious adverse outcomes from perioperative hypothermia are well documented. Consequently, intraoperative warming has become routine. We thus evaluated the efficacy of a novel, nondisposable carbon-fiber resistive-heating system. Twenty-four patients undergoing open abdominal surgery lasting approximately 4 h were randomly assigned to warming with 1) a full-length circulating water mattress set at 42°C, 2) a lower-body forced-air cover with the blower set on high, or 3) a three-extremity carbon-fiber resistive-heating blanket set to 42°C. Patients were anesthetized with a combination of continuous epidural and general anesthesia. All fluids were warmed to 37°C, and ambient temperature was kept near 22°C. Core (tympanic membrane) temperature changes among the groups were compared by using factorial analysis of variance and Scheffé F tests; results are presented as means ± SD. Potential confounding factors did not differ significantly among the groups. In the first 2 h of surgery, core temperature decreased by 1.9°C ± 0.5°C in the circulating-water group, 1.0°C ± 0.6°C in the forced-air group, and 0.8°C ± 0.2°C in the resistive-heating group. At the end of surgery, the decreases were 2.0°C ± 0.8°C in the circulating-water group, 0.6°C ± 1.0°C in the forced-air group, and 0.5°C ± 0.4°C in the resistive-heating group. Core temperature decreases were significantly greater in the circulating-water group at all times after 150 elapsed minutes; however, temperature changes in the forced-air and resistive-heating groups never differed significantly. Even during major abdominal surgery, resistive heating maintains core temperature as effectively as forced air.

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Even mild perioperative hypothermia causes numerous severe complications (1). Adverse consequences of mild hypothermia that have been proven in prospective, randomized trials include coagulopathy (2) and increased transfusion requirements (3), surgical wound infections and prolonged hospitalization (4,5), prolonged duration of recovery (6), shivering (7), thermal discomfort (8), and morbid myocardial outcomes (9). Consequently, it is now standard practice to maintain intraoperative normothermia unless hypothermia is specifically indicated.

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Numerous studies have demonstrated that circulating-water mattresses have limited efficacy (10). Furthermore, circulating water is associated with "pressure-heat necrosis" (i.e., burns) that result when tissue compressed by the weight of the patient is simultaneously warmed (11–14). Perioperative use of forced-air warming has thus become routine because it is both safer and far more effective than circulating water. However, disposable forced-air covers are relatively expensive.

Recently, an inexpensive, nondisposable resistive-warming system was developed. It is based on carbon-fiber technology and uses 15-V direct current. An advantage of the system is that it can independently heat numerous cover segments; consequently, a large fraction of the body surface can be warmed during almost any type of operation. This is a critical feature because routine heat loss (15,16) and heat transfer by clinical warmers (17) depend linearly on exposed surface area. To evaluate the efficacy of resistive heating, we compared

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core temperature changes during major abdominal surgery by using circulating-water, forced-air, and resistive heating.

Methods

With approval of the Ethics Committee at Tokyo Women's Medical University and with written, informed consent, we studied 24 patients undergoing elective open abdominal surgery. All were ASA physical status I or II and were aged 20–80 yr. Patients with preoperative fever, evidence of current infection, thyroid disease, or dysautonomia were excluded.

Patients were premedicated with 2–3 mg of midazolam and 0.5 mg of atropine 30 min before surgery. An epidural catheter was inserted at an interspace between T8 and L1 by using standard technique. Three milliliters of 2% lidocaine with epinephrine was given as a test dose; the catheter was subsequently injected with 7–10 mL of 0.5% bupivacaine with 2.5 μg/mL of fentanyl, and additional bupivacaine/fentanyl solution was injected as necessary to obtain a T4 to L1 sensory block level. Epidural anesthesia was maintained during surgery with a continuous infusion of bupivacaine (0.125%) and fentanyl (2.5 μg/mL) solution at a rate of 5–10 mL/h.

General anesthesia was induced with propofol 2 mg/kg and maintained with a propofol infusion combined with 60% nitrous oxide. Patients were paralyzed with vecuronium and mechanically ventilated to maintain end-tidal carbon dioxide partial pressure near 35 mm Hg. All fluids were warmed to 37°C, and ambient temperature was kept near 22°C.

Participating patients were randomly assigned to warming with 1) a full-length circulating-water mattress set to 42°C (Meditherm; Gaymar Industries, Inc., Orchard Park, NY) with a 5-mm pad placed between the circulating-water mattress and the patient to reduce the risk of burns (circulating-water group); 2) a lower-body forced-air cover with the controller set to high (Bair Hugger; Augustine Medical, Inc., Eden Prairie, MN) (forced-air group); or 3) a resistive-heating blanket set to 42°C (SmartCare OP System; Thermamed GmbH, Bad Oeynhausen, Germany) (resistive-heating group). The resistive-heating system covered one arm, the chest, and both legs. All warmers were started just before the induction of general anesthesia and were maintained throughout surgery. Randomization was based on computer-generated codes that were maintained in sequentially numbered opaque envelopes until just before the induction of anesthesia.

Demographic and morphometric characteristics of the participants were recorded. Vital signs were recorded at 15-min intervals. We also recorded the duration of surgery, fluid balance, and propofol dose. All temperatures were measured with Mon-a-Therm thermocouples (Tyco-Mallinckrodt, Inc., St. Louis, MO). Measurements started before the induction of anesthesia and continued throughout surgery at 15-min intervals.

Ambient temperature was measured with a thermocouple positioned at the level of the patient, but well away from any heat-producing equipment. Mean skin temperature was calculated from temperatures recorded at four cutaneous sites (18) by using the following formula:

$$\text{Mean skin temperature} = 0.3(T_{\text{chest}} + T_{\text{arm}}) + 0.2(T_{\text{thigh}} + T_{\text{calf}}) \quad (1)$$

Core temperature was measured at the tympanic membrane by using an aural probe. The probes were inserted by the patients until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected a gentle rubbing of the attached wire. The aural canal was then occluded with cotton, and the probe was taped in place.

Core temperatures are presented as a function of intraoperative time, with the induction of anesthesia considered elapsed Time 0. All other intraoperative measurements were averaged over time in each patient and then averaged among the patients given each treatment.

Differences among the groups were compared by using one-way analysis of variance and Scheffé F tests. Results are presented as means ± SD unless otherwise indicated; $P < 0.05$ was considered statistically significant.

Results

Eight patients were assigned to each group, and each was treated per protocol. Mean skin temperature was significantly lower in the circulating-water group compared with the other groups. Demographic and morphometric characteristics of the patients in each group were similar, as were surgical factors, ambient temperature, fluid balance, and vital signs (Table 1). No complications related to any of the warming methods were observed.

The duration of surgery averaged 240 min, and core temperature in each group decreased for the first hour. After 1 h of anesthesia, core temperature changes in the circulating-water, forced-air, and resistive-heating groups were −1.4°C ± 0.4°C, −1.1°C ± 0.5°C, and −0.9°C ± 0.3°C, respectively; these values did not differ significantly. Core temperature in the first 2 h of surgery decreased by 1.9°C ± 0.5°C in the circulating-water group, 1.0°C ± 0.6°C in the forced-air group, and 0.8°C ± 0.2°C

Table 1. Potential Confounding Factors

Variable	Group		
	Circulating water	Forced air	Carbon fiber
Age (yr)	59 ± 9	62 ± 14	66 ± 11
Sex (male/female)	5/3	5/3	5/3
Weight (kg)	52 ± 8	59 ± 11	58 ± 7
Body mass index ($kg \cdot m^{-2}$)	21 ± 2	22 ± 2	23 ± 2
Surgical duration (min)	208 ± 51	248 ± 96	253 ± 69
Ambient temperature (°C)	22 ± 1	22 ± 1	22 ± 1
Heart rate (bpm)	77 ± 15	78 ± 11	70 ± 12
Mean arterial pressure (mm Hg)	83 ± 11	80 ± 9	84 ± 10
Spo_2 (%)	99.6 ± 0.6	99.1 ± 1.5	99.9 ± 0.3
End-tidal Pco_2 (mm Hg)	32 ± 2	33 ± 1	31 ± 4
Administered fluid ($mL \cdot kg^{-1} \cdot h^{-1}$)	21 ± 7	17 ± 8	14 ± 5
Urine output ($mL \cdot kg^{-1} \cdot h^{-1}$)	5 ± 4	5 ± 6	5 ± 3
Blood loss ($mL \cdot kg^{-1}$)	12 ± 9	12 ± 16	7 ± 8
Propofol ($mg \cdot kg^{-1} \cdot h^{-1}$)	6 ± 2	6 ± 2	6 ± 2

None of the values differed significantly among the treatment groups. Data presented as means ± SD.

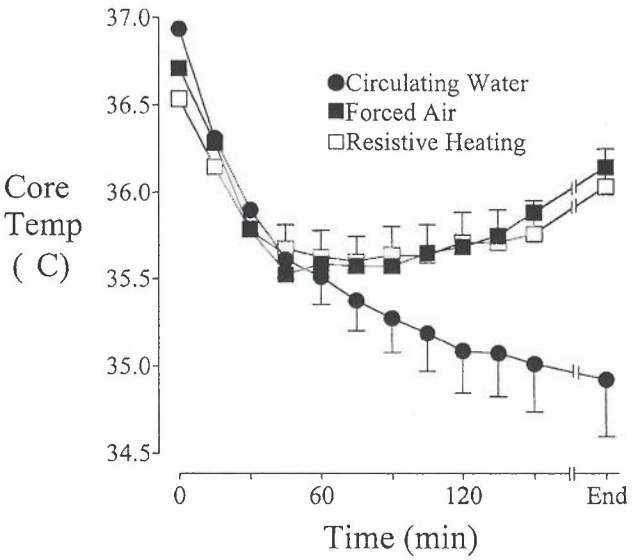

Figure 1. Core temperature as a function of time in patients assigned to the circulating-water, forced-air, and resistive-heating groups. All groups had an *n* of 8 except at 150 min, when the circulating-water and forced-air groups each had an *n* of 7. Temperature changes in the circulating-water group differed significantly from those in the other groups after 150 elapsed minutes. Temperatures in the forced-air and resistive-heating groups never differed significantly. Results are presented as means ± SEM.

in the resistive-heating group. Core temperature then increased for the duration of surgery in the forced-air and resistive-heating groups but continued to decrease in the patients assigned to circulating water (Fig. 1). On completion of surgery, core temperature was 34.9°C ± 0.9°C in the circulating-water group, 36.2°C ± 1.0°C in the forced-air group, and 36.0°C ± 0.6°C in the resistive-heating group. This corresponds to temperature changes of −2.0°C ± 0.8°C in the circulating-water group, −0.6°C ± 1.1°C in the forced-air group, and −0.5°C ± 0.4°C in the resistive-heating group. Core temperature changes were significantly greater in the circulating-water group at all times after 150 elapsed minutes; however, those in the forced-air and resistive-heating groups never differed significantly.

Discussion

Redistribution is usually the most important cause of hypothermia during general (19) or neuraxial (20) anesthesia. This rapid core-to-peripheral transfer of heat makes nearly all patients hypothermic, including those undergoing relatively short, small procedures. Redistribution hypothermia is difficult to treat because it results from a large internal flow of heat rather than net exchange of heat with the environment. Redistribution can, though, be prevented by preinduction warming (21,22) or by inducing pharmacologic vasodilation well before the induction of anesthesia (23).

Our results are consistent with previous observations: core temperatures in each of the three treatment groups decreased at least 1°C during the first hour of anesthesia. Core temperature in the circulating-water group continued to decrease for the remainder of surgery, which is consistent with numerous previous studies showing that circulating-water mattresses are virtually ineffective (10,24,25). In contrast, core temperature in the remaining patients increased throughout the remainder of surgery. As a result, patients in both these treatment groups were nearly normothermic at the end of anesthesia.

The temperature profiles were virtually identical in the forced-air and resistive-heating groups. Although a statistically significant difference might have been detected with a very large number of patients, it is clear

that there was no clinically important difference between these methods. Intraoperative core-temperature perturbations depend on numerous factors, including ambient temperature, the type of surgery, and morphometric characteristics. Absolute temperature changes would thus presumably vary in other circumstances. However, our conclusion that forced-air and resistive-heating warmers are comparably effective and far more effective than circulating-water mattresses would presumably remain accurate.

Our patients were at special risk for hypothermia because they had open abdominal surgery. Not surprisingly, patients having large, long operations are at greater risk of hypothermia than those having smaller procedures; however, they were also at special risk because general and epidural anesthesia were combined. All general anesthetics produce a dose-dependent inhibition of thermoregulatory control (1). This produces hypothermia in a typical cool operating room environment. Hypothermia, though, is limited because patients who become sufficiently cold (usually near 34°C) trigger thermoregulatory vasoconstriction that produces a core-temperature plateau (26). Neuraxial anesthesia similarly inhibits central thermoregulatory control (27,28) by an amount that depends on block height (29). More importantly, however, epidural anesthesia usually also produces a lower-body sympathectomy. Severe hypothermia is thus especially likely when general and epidural anesthesia are combined, because epidural-induced sympathectomy prevents the core-temperature plateau (30).

Cutaneous heat loss is a nearly linear function of body surface area with (15) and without (16) anesthesia. The efficacy of passive insulation (31,32) or active clinical warming systems (17) is thus proportional to available skin surface. An advantage of the resistive-heating segment system is the flexibility to cover large amounts of surface area. Flexibility in positioning multiple independent heating segments is especially likely to be valuable in operations that leave limited surface area available for warming. Furthermore, the individual segments are relatively small, so they do not interfere with positioning of monitors or IV catheters. A corollary is that systems that cover a larger surface area will transfer more total heat at a given heat transfer rate or be able to transfer comparable amounts of heat at low (and therefore safer) system temperatures.

Resistive heating is a relatively new patient-warming system but has nonetheless been evaluated in several previous studies. Greif et al. (33), for example, tested resistive heating in a model of accidental hypothermia. Active warming proved far more effective than reflective covers ("space blankets"). Resistive heating has also been used during transport of trauma victims (34). Again, it proved far more effective than metallic-foil insulation. Interestingly, active warming not only improved thermal comfort and increased core temperature, but also reduced pain and improved overall patient satisfaction.

The resistive-heating system we tested is powered from electrical mains, but the current is converted into a smooth 15-V supply within the controller. The system is fully isolated and meets all relevant electrical safety standards. Up to 6 segments can be connected to a single controller (12 × 12 × 23 cm; 2 kg). The heating elements consist of special semiconducting carbon-fiber fabric strips. Each strip has two thermistors: one is used to servocontrol strip temperature, and the other is a backup safety system that is completely independent of the central controller.

Unlike nearly all forced-air systems, resistive heating does not require a disposable element. Once acquired, there is no substantial additional cost of using the system. Resistive heating is thus likely to prove considerably less expensive than forced air in routine use. The heating segments are covered with a washable cover that has an antibacterial coating, is fluid resistant, and can be sterilized or disinfected simply by wiping with a disinfectant solution.

An American Society of Anesthesiologists closed-claims study reported 54 burns among 3000 anesthesia claims. Patient warming devices caused 28 burns, with circulating-water mattresses being responsible for 5 of them (35). More importantly, the "pressure-heat necrosis" associated with circulating-water mattresses may not be apparent until many days after surgery and is often considered a pressure ulcer rather than a burn (11,12). It is thus routine to position a thin pad between circulating-water mattresses and the patients. We also covered the circulating-water mattress with a pad; a limitation of this approach is that the pad reduces heat transfer. It is thus likely that efficacy of the circulating-water mattress would have been greater without the pad. Efficacy of circulating water was nonetheless poor in previous studies in which insulation was restricted to a single sheet (10). It thus seems unlikely that our use of a pad markedly altered our results. Potential confounding factors were similar in the three treatment groups. It is thus unlikely that any contributed significantly to our results.

In summary, the adverse effects of mild perioperative hypothermia are well documented. Consequently, it is now standard to maintain intraoperative normothermia unless hypothermia is specifically indicated. Core temperatures were similar with forced-air and resistive-heating warming but were significantly less with circulating water. We thus conclude that, even during major abdominal surgery, resistive heating maintains core temperature as effectively as forced air. Resistive heating does not require a disposable component and is thus less expensive than forced air in routine use.

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